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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,797	SIEGLER, KATHERINE MEYER	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-93* is/are pending in the application.

4a) Of the above claim(s) *6-10,16-22 and 24-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11-15 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed December 14, 2006, is acknowledged and has been entered. Claim 1 has been amended.

2. The declaration under 37 C.F.R. § 1.131 by Katherine L. Meyer-Siegler, Ph.D., filed December 13, 2006, is acknowledged and has been entered.

3. Claims 1-93 are pending in the application. Claims 6-10, 16-22, and 24-93 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 9, 2006.

4. Claims 1-5, 11-15, and 23 are currently under prosecution.

5. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Grounds of Objection and Rejection Withdrawn

6. Unless specifically reiterated below, Applicant's amendment and/or arguments submitted December 14, 2006, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed September 15, 2006.

Response to Declaration

7. The declaration under 37 C.F.R. § 1.131 by Katherine L. Meyer-Siegler, Ph.D., has been found sufficient to overcome the rejection of claims 1-3, 11-15, and 23 under 35 U.S.C. § 102(a), as being anticipated by Meyer-Siegler et al. (*Cancer.* 2002 Mar 1; **94** (5): 1449-1456), for the reasons set forth in sections 15 of the preceding Office action mailed September 15, 2006.

Grounds of Rejection Maintained

Specification

8. The objection to the specification, as failing to provide proper antecedent basis for the claimed subject matter, is maintained. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

(a) Claim 5 is directed to the method of claim 2, wherein the immunoassay is a protein array. At paragraph [0037] of the published application[1], the specification discloses the nucleic acid hybridization assay may involve the use of probes immobilized on solid supports, such as microarrays; but the specification does not describe an immunoassay that is, or comprises the use of a protein array.

Notably, Applicant has traversed this ground of objection, arguing at page 18 of the amendment filed December 14, 2006, that a protein array is well known in the art, and one skilled in the art would know how to practice the claimed invention using a protein array without further description.

Applicant's argument has been considered but is immaterial to the issue. The language of the claims must find written support in the disclosure, since otherwise the disclosure would fail to provide the requisite antecedent basis for that claim language. Because claim 5 is an original claim, Applicant may remedy this issue by amending the disclosure to provide written support for the language of the claim. For example, this issue might be remedied if Applicant were to amend the specification at paragraph [0033] of the published application to read, where the suggested change is underlined:

> In an embodiment of the present invention, serum MIF levels are detected by immunoassays. Generally, immunoassays involve the binding of the MIF and anti-MIF antibody. The presence and amount of binding indicate the presence and amount of MIF present in the sample. Examples of immunoassays include, but are not limited to, protein arrays, ELISAs, radioimmunoassays, and immunoblots, which are well known in the art. The antibody can be polyclonal or monoclonal and is preferably labeled for easy detection. The labels can be, but are not limited to biotin, fluorescent molecules, radioactive molecules, chromogenic substrates, chemi-luminescence, and enzymes.

[1] U.S. Patent Application Publication No. 2004/0171021 A1.

(b) Claim 23 is directed to the method of claim 1, further comprising the step of comparing the levels of MIF in the serum of the individual to the MIF levels of prostate cancer patients. The specification, however, fails to provide proper antecedent basis for the claimed subject matter.

At page 19 of the amendment filed December 14, 2006, Applicant has traversed this ground of objection, arguing that the disclosure provides antecedent basis for the language of claim 23 in Example 2 (paragraphs [0054]-[0058] of the published application).

Applicant's argument has been considered but not found persuasive. Contrary to Applicant's assertion, the disclosure of Example 2 does not provide written support for the language of claim 23 because it does not describe a method for detecting or diagnosing prostate cancer in an individual comprising the step of determining levels of MIF in the serum of the individual, and further comprising the step of comparing the levels of MIF in the serum of the individual to the MIF levels of prostate cancer patients, wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer. Rather, Example 2 describes an analysis of the levels of MIF in the sera of patients previously diagnosed as having benign prostatic hyperplasia (BPH), prostate cancer, or high-grade prostate intraepithelial neoplasia (HGPIN), or in the sera of other available patients that were not diagnosed or reported to have any known prostate pathologies.

Again, because claim 23 is an original claim, this issue may be remedied by amending the disclosure to provide the requisite antecedent basis for the language of the claim.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. The rejection of claims 1-5, 11-15, and 23 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

At page 19 of the amendment filed December 14, 2006, Applicant has traversed this ground of rejection.

Applicant's argument have been carefully considered but not found persuasive for the following reason:

Applicant has contended that this issue has been obviated by the amendment to claim 1.

Contrary to Applicant's position, however, claims 1-5, 11-15, and 23, as presently amended, remain indefinite for the following reasons:

Claim 1 fails to recite an active process step that positively relates back to the objective of the invention, as recited in the preamble of the claim. The claim is directed to a method for detecting or diagnosing prostate cancer in an individual; yet, the claim merely recites the process comprises the step of determining levels of MIF in the serum of the individual, wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer. There is no active process step that clearly relates back to the purpose or objective of the claimed invention, namely the detection or diagnosis of prostate cancer in the individual, and thus while the intended use of the claimed invention is to detect or diagnose prostate cancer, it would appear that the process itself would not necessarily achieve that objective. The phrase "wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer" merely describes a "result", but does not unambiguously require the practitioner of the invention to measure serum levels of MIF that fall within this range to necessarily provide the practitioner with the indication that the individual prostate cancer. Consequently, it is submitted that the skilled artisan could not determine whether each and every process step considered essential to the practice of the claimed invention has been included in the body of the claim. For example, as claimed, the invention cannot be distinguished from the manipulatively identical processes disclosed by the prior art (e.g., Mitamura et al. [of record], where the process resulted in a determination that MIF levels in the sera of patients with proliferative diabetic retinopathy and controls fell within the specified range (7.17 and 5.76 ng/ml, respectively), yet none of whom were diagnosed as having prostate cancer). As such, because of the absence of a correlative active step, which manipulatively defines the process as a method for detecting or diagnosing prostate cancer, and which positively relates the whole of the process to its intended use, as recited in the preamble, claim 1 fails to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the

requirement set forth under 35 U.S.C. § 112, second paragraph, as the objective to practicing the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The rejection of claims 1-3 and 11-13 uunder 35 U.S.C. 102(a), as being anticipated by Zhang et al. (*Hepatobiliary Pancreat. Dis. Int.* 2002 Nov; 1 (4): 577-580), is maintained.

Beginning at page 20 of the amendment filed December 14, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reason:

Applicant has argued that Zhang et al. does not teach the detection or diagnosis of prostate cancer in an individual.

However, inasmuch as the claimed invention is intended for use in detecting or diagnosing prostate cancer, any anticipatory process disclosed by the prior art need only be suitable for use in detecting or diagnosing prostate cancer in an individual.

Zhang et al. teaches measuring the levels of MIF in the serum of individuals; see entire document (e.g., the abstract). Zhang et al. teaches the measurement was made using an ELISA; see, e.g., the abstract; and page 578, column 1.

The process described by the prior art is manipulatively identical to the process that is claimed.

As explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, the recitation of the phrase "wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer" merely describes a "result" that is

achievable by practicing the process steps recited in the body of the claim, but *does not limit* the claimed process, as the claim does not require the practitioner of the invention to measure serum levels of MIF that fall within this range to necessarily provide the practitioner with the indication that the individual prostate cancer.

Arguably, it is submitted that, at best, the recitation in claim 1 of the phrase, "wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer" would necessitate that there be a mere possibility that the levels of MIF in the sera of the individual fall within the recited range, since otherwise such a process might not be used in a manner that would at least be consistent with its intended purpose. Therefore, it is aptly noted that the process described by the prior art resulted in a determination that MIF levels in the sera of controls patients controls fell within the specified range of between about 5 and 10 ng/ml (i.e., 4.06 ± 0/71 ng/ml; see, e.g., page 578, Table), and that the levels of MIF in the sera of patients diagnosed with liver disease (i.e., chronic hepatitis or hepatitis cirrhosis with or without ascites) were substantially elevated above the level in the control sera (page 578, Table).

13. The rejection of claims 1-3 and 11-15 under 35 U.S.C. 102(b), as being anticipated by Mitamura et al. (*Br. J. Ophthalmol.* 2000; **84**: 636-639), is maintained.

Beginning at page 20 of the amendment filed December 14, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reason:

Applicant has argued that Mitamura et al. does not teach the detection or diagnosis of prostate cancer in an individual.

However, inasmuch as the claimed invention is intended for use in detecting or diagnosing prostate cancer, any anticipatory process disclosed by the prior art need only be suitable for use in detecting or diagnosing prostate cancer in an individual.

Mitamura et al. teaches measuring the levels of MIF in the serum of individuals; see entire document (e.g., the abstract). Mitamura et al. teaches the measurement was made using an ELISA; see, e.g., the abstract; and page 637, paragraph bridging columns. Mitamura et al.

teaches the ELISA utilized a biotin-labeled antibody that specifically binds MIF; see, e.g., page 637, column 2.

The process described by the prior art is manipulatively identical to the process that is claimed.

As explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, the recitation of the phrase "wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer" merely describes a "result" that is achievable by practicing the process steps recited in the body of the claim, but *does not limit* the claimed process, as the claim does not require the practitioner of the invention to measure serum levels of MIF that fall within this range to necessarily provide the practitioner with the indication that the individual prostate cancer.

Arguably, it is submitted that, at best, the recitation in claim 1 of the phrase, "wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer" would necessitate that there be a mere possibility that the levels of MIF in the sera of the individual fall within the recited range, since otherwise such a process might not be used in a manner that would at least be consistent with its intended purpose. Therefore, it is aptly noted that the process described by the prior art resulted in a determination that resulted in a determination that MIF levels in the sera of patients with proliferative diabetic retinopathy and controls fell within the specified range (7.17 and 5.76 ng/ml, respectively); see, e.g., page 638, column 1.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The rejection of claims 1, 2, and 4 under 35 U.S.C. 103(a), as being unpatentable over Mitamura et al. (*Br. J. Ophthalmol.* 2000; **84**: 636-639) in view of Leech et al. (*Arthritis Rheumatol.* 2000 Apr; **43** (4): 827-833), is maintained.

Beginning at page 21 of the amendment filed December 14, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reason:

Here, claims 1, 2, and 4 are directed to the method of claim 4.

Applicant has argued that neither reference teaches the detection or diagnosis of prostate cancer in an individual.

However, inasmuch as the claimed invention is intended for use in detecting or diagnosing prostate cancer, any process rendered obvious by the prior art over a combination of references need only be suitable for use in detecting or diagnosing prostate cancer in an individual.

Mitamura et al. teaches that which is set forth in the above rejection of claims 1-3 and 11-15 35 U.S.C. 102(b).

Notably, the process described by the prior art resulted in a determination that resulted in a determination that MIF levels in the sera of patients with proliferative diabetic retinopathy and controls fell within the specified range (7.17 and 5.76 ng/ml, respectively); see, e.g., page 638, column 1. Accordingly, it is submitted that the process is suitable for use in detecting or diagnosing prostate cancer in an individual.

Then, as explained in the preceding Office action, although Mitamura et al. does not teach measuring the levels of MIF in the serum of individuals using an immunblot assay, Leech et al. teaches measuring the levels of MIF in the serum of individuals using an immunblot assay.

Therefore, as also explained previously, it would have been obvious to one ordinarily skilled in the art at the time of the invention to have measured the level of MIF in the serum of the individual using an immunoblot assay because Leech et al. teaches such an assay is used to do so. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to determine the level of MIF in the serum of the individual.

Furthermore, in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

16. The rejection of claims 1, 2, and 5 under 35 U.S.C. 103(a), as being unpatentable over Mitamura et al. (*Br. J. Ophthalmol.* 2000; **84**: 636-639) in view of Wright et al. (*Prostate Cancer Prostatic Dis.* 1999 Dec; **2** (5/6): 264-76), is maintained.

Beginning at page 21 of the amendment filed December 14, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reason:

Here, claims 1, 2, and 5 are directed to the method of claim 5.

Applicant has argued that neither reference teaches the detection or diagnosis of prostate cancer in an individual.

However, inasmuch as the claimed invention is intended for use in detecting or diagnosing prostate cancer, any process rendered obvious by the prior art over a combination of references need only be suitable for use in detecting or diagnosing prostate cancer in an individual.

Mitamura et al. teaches that which is set forth in the above rejection of claims 1-3 and 11-15 35 U.S.C. 102(b).

Notably, the process described by the prior art resulted in a determination that resulted in a determination that MIF levels in the sera of patients with proliferative diabetic retinopathy and controls fell within the specified range (7.17 and 5.76 ng/ml, respectively); see, e.g., page 638, column 1. Accordingly, it is submitted that the process is suitable for use in detecting or diagnosing prostate cancer in an individual.

Then, as explained in the preceding Office action, although Mitamura et al. does not teach measuring the levels of MIF in the serum of individuals using a protein array, Wright et al. teaches measuring the levels of serum biomarkers using a protein array; see entire document (e.g., the abstract). Wright et al. teaches improved early detection and diagnosis will require the

use of such rapid and high throughput technology, which enables the detection of multiple markers; see, e.g., the abstract.

Therefore, as also explained previously, it would have been obvious to one ordinarily skilled in the art at the time of the invention to have measured the level of MIF in the serum of the individual using a protein array because Wright et al. teaches the use of such arrays provides rapid and high throughput detection of multiple markers, which will improve early detection and diagnosis of disease associated with the presence of the markers in the serum. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to improve early detection and diagnosis of disease associated with the presence of the markers in the serum.

Furthermore, in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

17. The rejection of claims 1-4, 11-13, and 23 under 35 U.S.C. 103(a), as being unpatentable over U.S. Patent No. 6,043,044 A (of record; cited by Applicant) in view of Koong et al. (*Cancer Res.* 2000 Feb 15; **60**: 883-887) and Meyer-Siegler (*J. Interferon Cytokine Res.* 2000; **20**: 769-778), is maintained.

Beginning at page 21 of the amendment filed December 14, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reason:

Applicant has argued that Meyer-Siegler discloses that prostate cell secrete MIF in cell culture, not *in vitro*; however, cell culture is performed *in vitro*.

Applicant has argued that the allegation that the invention would have been obvious given the combination of the teachings of the references is erroneous because Koong et al. does not teach that MIF is detectable in blood serum.

In response, as explained in the preceding Office action, U.S. Patent No. 6,043,044 A (Hudson et al.) teaches detecting and diagnosing prostate cancer in a subject by a process comprising measuring the levels of MIF within the subject's tissues or cells and comparing those

levels to the levels of MIF in appropriate positive and/or negative control cells; see entire document (e.g., column 1, line 60, through column 2, line 24; column 2, lines 62-65; column 3, lines 1-25 and Table 1; and claims 1-3). Although Hudson et al. does not teach detecting and/or diagnosing prostate cancer in a subject by measuring the levels of MIF within the subject's serum, Koong et al. teaches MIF is overexpressed in cancer cells; see entire document (e.g., the abstract; page 885, Table 1; and page 886, column 1 and 2). Koong et al. teaches another protein, namely PAI-1, which is also overexpressed in cancer cells; see, e.g., page 885, Table 1. Koong et al. teaches because PAI-1 is a secreted protein, serum levels are readily detectable and may be used as a molecular marker; see, e.g., page 883, column 2. Moreover, Koong et al. teaches because PAI-1 is a secreted protein, serum levels can be monitored in a relatively noninvasive manner to determine or detect early subclinical recurrence of the disease associated with its overexpression; see, e.g., page 885, column 2. Then, Meyer-Siegler teaches prostate epithelial cells secrete MIF; and moreover, Meyer-Siegler teaches prostate cancer cells secrete more MIF than normal prostate cells (see, e.g., the abstract). Accordingly, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have detected and/or diagnosed prostate cancer in a subject by measuring the levels of MIF within the subject's serum and comparing the determined levels to appropriate negative and/or positive controls, such as the levels of MIF in the sera of subject known not to have prostate cancer or the sera of subjects already diagnosed with prostate cancer, because Hudson et al. teaches MIF is overexpressed in prostate cancer, as compared to normal prostate, Meyer-Siegler teaches MIF is secreted by prostate epithelial cells, including prostate cancer cells, which secrete relatively more MIF than normal prostate cells, and Koong et al. teaches since a tumor antigen, such as MIF, is overexpressed and secreted by cancer cells, its presence in the serum of subject's afflicted by the disease is readily determined. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to detect and/or diagnose prostate cancer in an individual, and more particularly because Koong et al. teaches the serum levels of such tumor antigens are monitored in a relatively noninvasive manner to permit determination or detection of early subclinical recurrence of the disease.

In further response to Applicant's arguments against any of the references individually, one cannot show nonobviousness by attacking references individually where the rejections are

based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In addition, Applicant has argued that Meyer-Siegler does to teach that prostate cancer cells secrete MIF *in vivo*, and that because the cell culture was grown and maintained in an artificial environment, which does not approximate conditions *in vivo*, there would be no reasonable expectation of success because it would not be known whether the MIF is secreted by the cells *in vivo*.

The Examiner disagrees. Contrary to Applicant's assertion, it is submitted that there would be no reason to expect the cultured prostate cancer cells, which secrete MIF, would not have done so *in vivo*, despite that fact that cell culture conditions differ from conditions under which the same cells were found *in vivo*. Applicant's contention is based upon an apparent presumption that the secretion of MIF by cultured prostate cancer cells is an artifact caused by their removal from the body and/or the conditions under which they were subsequently placed; however, Applicant has provided no factual evidence to support such a presumption, but only remarked there are a multitude of biological processes that may prevent MIF from showing up in the serum. In response, therefore, Applicant is invited to name one or more of such biological processes that may prevent MIF from showing up in the serum, when the prostate cancer cells are present in the body.

Furthermore, Applicant has argued that Hudson et al. teaches against measuring MIF in the serum because it is also expressed in, or by the brain, eye lenses, fibroblasts, testes, and pituitary; and so Applicant has queried, if MIF were present in the serum, how would one know if its presence in the serum was the result of its expression by prostate cancer cells, as opposed to other types of cells?

U.S. Patent No. 6,043,044 A (Hudson et al.) teaches detecting and diagnosing prostate cancer in a subject by a process comprising measuring the levels of MIF within the subject's tissues or cells and comparing those levels to the levels of MIF in appropriate positive and/or negative control cells. Notably, Hudson et al. does not teach detecting and/or diagnosing prostate cancer in a subject by measuring the levels of MIF within the subject's serum; but nonetheless, in addition to teaching that MIF is overexpressed in cancer cells, Koong et al. teaches levels of tumor-associated antigens, which are secreted by the tumors into the serum, can

be monitored in a relatively noninvasive manner to determine or detect early subclinical recurrence of the disease associated with their overexpression, and then Meyer-Siegler teaches prostate cancer cells secrete more MIF than normal prostate cells, and that prostate epithelial cells secrete MIF. So in response to Applicant's query, while there is factual evidence that prostate cancer cells overexpress MIF and that these cells secrete MIF, none of Hudson et al., Koong et al., and Meyer-Siegler teach or suggest that any of these other types of cells that are also described by Hundson et al. as capable of expressing MIF (e.g., fibroblasts) secrete detectable levels of the protein into the serum. Therefore, it would only be reasonable to conclude the presence in the serum of MIF resulted from its expression by prostate cancer cells, as it would not be reasonable to otherwise conclude that its presence in the serum resulted from its expression by any of the other types of cells mentioned by Hudson et al.

Finally, Applicant has remarked that none of the cited references upon which the ground of rejection is based teaches that serum levels of MIF in the range of about 5 to about 10 ng/ml indicated the presence of prostate cancer.

In response, as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, the recitation of the phrase "wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer" merely describes a "result" that is achievable by practicing the process steps recited in the body of the claim, but *does not limit* the claimed process, as the claim does not require the practitioner of the invention to measure serum levels of MIF that fall within this range to necessarily provide the practitioner with the indication that the individual prostate cancer. Therefore, any process rendered obvious by the prior art over a combination of references need only be suitable for use in detecting or diagnosing prostate cancer in an individual.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

18. Claims 1, 2, 4, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Leech et al. (*Arthritis Rheumatol.* 2000 Apr; **43** (4): 827-833) (of record), as evidenced by Mitamura et al. (*Br. J. Ophthalmol.* 2000; **84**: 636-639) (of record).

Leech et al. teaches measuring the levels of MIF in the serum of individuals; see entire document (e.g., the abstract). Leech et al. teaches the measurement was made using an immunblot (i.e., Western blot) assay; see, e.g., the abstract.

It is submitted that, inasmuch as the claimed invention is intended for use in detecting or diagnosing prostate cancer, any anticipatory process disclosed by the prior art need only be suitable for use in detecting or diagnosing prostate cancer in an individual.

The process described by the prior art is manipulatively identical to the process that is claimed.

Notably, claim 1 has been amended to recite, "wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer". However, as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, the recitation of the phrase merely describes a "result" that is achievable by practicing the process steps recited in the body of the claim, but *does not limit* the claimed process, as the claim does not require the practitioner of the invention to measure serum levels of MIF that fall within this range to necessarily provide the practitioner with the indication that the individual prostate cancer.

Arguably, it is submitted that, at best, the recitation in claim 1 of the phrase, "wherein serum MIF levels of greater than about 5 to about 10 ng/ml indicates the presence of prostate cancer" would necessitate that there be a mere possibility that the levels of MIF in the sera of the individual fall within the recited range, since otherwise such a process might not be used in a manner that would at least be consistent with its intended purpose. Therefore, as evidenced by Mitamura et al., the measurement of the levels of MIF in the serum of individuals using an ELISA resulted in a determination that MIF levels in the sera of patients with proliferative diabetic retinopathy and controls fell within the specified range (7.17 and 5.76 ng/ml, respectively); see, e.g., page 638, column 1. Accordingly, the process disclosed by Leech et al. is deemed the same as the claimed process, since as evidenced by Mitamura et al. that process is suitable for use in detecting or diagnosing prostate cancer in an individual.

Claim Rejections - 35 USC § 103

19. Claims 1-4, 11-13, and 23 are rejected under 35 U.S.C. 103(a), as being unpatentable over U.S. Patent No. 6,043,044 A (of record; cited by Applicant) in view of Koong et al. (*Cancer*

Res. 2000 Feb 15; **60**: 883-887) (of record), Meyer-Siegler (*J. Interferon Cytokine Res.* 2000; **20**: 769-778) (of record), and Arcuri et al. (*Prostate.* 1999; **39**: 159-165) (of record), as evidenced by Meyer-Siegler et al. (*BMC Cancer.* 2005 Jul 6; **5** (1): 73; copy of electronically published document, pp. 1-12).

U.S. Patent No. 6,043,044 A (Hudson et al.) teaches detecting and diagnosing prostate cancer in a subject by a process comprising measuring the levels of MIF within the subject's tissues or cells and comparing those levels to the levels of MIF in appropriate positive and/or negative control cells; see entire document (e.g., column 1, line 60, through column 2, line 24; column 2, lines 62-65; column 3, lines 1-25 and Table 1; and claims 1-3). Hudson et al. teaches the measurement is made using an ELISA or an immunoblot; see, e.g., column 4, lines 39-67; and column 5, lines 4-32. Hudson et al. teaches comparing the levels of MIF in the tissue or cell samples of an individual to the levels of MIF in prostate cancer patients; see, e.g., column 3, Table 1.

Hudson et al., however, does not teach detecting and/or diagnosing prostate cancer in a subject by measuring the levels of MIF within the subject's serum, and moreover Hudson et al. does not teach that serum MIF levels of greater than about 5 to about 10 ng/ml are detectable in subjects afflicted with the disease.

Koong et al. teaches MIF is overexpressed in cancer cells; see entire document (e.g., the abstract; page 885, Table 1; and page 886, column 1 and 2). Koong et al. teaches another protein, namely PAI-1, which is also overexpressed in cancer cells; see, e.g., page 885, Table 1. Koong et al. teaches because PAI-1 is a secreted protein, serum levels are readily detectable and may be used as a molecular marker; see, e.g., page 883, column 2. Moreover, Koong et al. teaches because PAI-1 is a secreted protein, serum levels can be monitored in a relatively noninvasive manner to determine or detect early subclinical recurrence of the disease associated with its overexpression; see, e.g., page 885, column 2. Koong et al. teaches measurements of the tumor antigens are made using an ELISA; see, e.g., page 884, the paragraph bridging columns.

Meyer-Siegler teaches prostate epithelial cells secrete MIF; see entire document (e.g., the abstract). Moreover, Meyer-Siegler teaches prostate cancer cells secrete more MIF than normal prostate cells; see, e.g., the abstract.

Arcuri et al. teaches MIF is localized to the microvilli of the secretory luminal prostatic epithelium and secreted into all prostatic fluids examined; see entire document (e.g., the abstract; page 160, column 1; page 161, column 1; page 162, Figure 1; and page 163, column 1). Arcuri et al. teaches: "The results of the present paper support the concept that prostate epithelial cells can secrete MIF" (page 163, column 1). Furthermore, Arcuri et al. teaches: "The present study demonstrated that the human prostate is a site of MIF synthesis" (page 163, column 2).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have detected and/or diagnosed prostate cancer in a subject by measuring the levels of MIF within the subject's serum and comparing the determined levels to appropriate negative and/or positive controls, such as the levels of MIF in the sera of subject known not to have prostate cancer or the sera of subjects already diagnosed with prostate cancer, because Hudson et al. teaches MIF is overexpressed in prostate cancer, as compared to normal prostate, because both Meyer-Siegler and Arcuri et al. teach MIF is secreted by prostate epithelial cells, where Meyer-Siegler further teaches prostate cancer cells secrete relatively more MIF than normal prostate cells, and because Koong et al. teaches since a tumor antigen, such as MIF, is overexpressed and secreted by cancer cells, its presence in the serum of subject's afflicted by the disease is readily determined. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to detect and/or diagnose prostate cancer in an individual, and more particularly because Koong et al. teaches the serum levels of such tumor antigens are monitored in a relatively noninvasive manner to permit determination or detection of early subclinical recurrence of the disease.

Meyer-Siegler et al. (2005) teaches median serum MIF levels in patients afflicted by prostate cancer are significantly elevated in prostate cancer patients (i.e., 5,87 ± 3.91 ng/ml), as compared to patients with no documented diagnosis of the disease; and accordingly, as evidenced by Meyer-Siegler et al. (2005), serum MIF levels of greater than about 5 to about 10 ng/ml are detectable in subjects afflicted with the disease.

Conclusion

20. No claim is allowed.

21. The art made of record and not relied upon is considered pertinent to Applicant's disclosure. Meyer-Siegler et al. (*Diagn. Mol. Pathol.* 1998 Feb; **7** (1): 44-50) teaches expression of MIF in the human prostate. Maaser et al. (*Gastroenterology*. 2002 Mar; **122** (3): 667-680) teaches ubiquitous production of MIF by gastric and intestinal epithelium. He et al. (*Gut*. 2006; **55**: 797-802) teaches increased epithelial and serum expression ofMIF in gastric cancer. Muramaki et al. (*Oncol. Rep.* 2006; **15**: 253-257) teaches the use of serum MIF in men with prostate cancer as a biomarker. Michael et al. (*Prostate*. 205; **62**: 34-39) teaches the diagnostic invalidity of serum MIF in patients with prostate cancer. Kitaichi et al. (*Graefe's Arch. Clin. Exp. Ophthalmol.* 2006; **244**: 825-828) teaches MIF expression in lacrimal fluid of patients with severe atopic dermatitis. Chen et al. (*Am. J. Trop. Med. Hyg.* 2006; **74** (1): 142-147) teaches serum levels of MIF in patients infected by dengue viruses. Kibiki et al. (*Clin. Immunol.* 2007; in press; copy of electronically published document, pp. 1-6) teaches serum and BAL MIF levels in patients infected with HIV. Rahman et al. (*Annals Surg.* 2007 Feb; **245** (2): 282-289) teaches serum MIF is a marker of pancreatic necrosis. Yanagi et al. (*Cytokine*. 2006; **35**: 270-274) teaches MIF is a proinflammatory cytokine present in the serum of patients afflicted with contact dermatitis.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
February 20, 2007